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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W., SUITE 600
WASHINGTON, DC 20005-3934

EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/11/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/826,210	SPRINGER et al.
Examiner	**Art Unit**
Christine Saoud	1647

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 18, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *39, 41, 42, and 48-83* is/are pending in the application.

4a) Of the above, claim(s) *41-42, 48-53, 82-83 (see action for details)* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *39 and 54-81 (in so far as they read on the elected invention)* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 76-83 have been added as requested in the amendment of paper #6, filed 18 June 2002. Claims 39, 41-42, 48-83 are pending in the instant application.

Election/Restriction

2. Applicant's election with traverse of Group I, claims 39, 54-75, in so far as they are directed to a method of stimulating cell division, in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I-VIII are related. This is not found persuasive because although the Groups utilize the same compound, the methods are distinct because they require treatment of different conditions, requiring different patient populations, they require different outcomes based on the condition being treated, and therefore, require separate searches. For example, administration of a compound for the treatment of a wound does not make obvious use of that compound for the treatment of a neural injury. Likewise, the fact that a cell stimulates cell division does not make obvious a method of treating heart disease. The searches for each of the methods are separate and distinct because the conditions which are being treated are separate and distinct. As stated previously, the methods have different functions and effects, based on the preamble of the claims and/or administration to different cell populations of the claims. Burden is established based on the necessity for non-coextensive literature searches. Applicant asserts that because each of the inventions are classified similarly, that they "can clearly be examined without

a serious burden on the part of the Examiner". This assertion is not persuasive for the reasons stated above, specifically that a search for each patient population is required, and each patient population is different for each claimed method, represented by Groups I-VIII.

Lastly, Applicant argues that restriction practice is not applicable to a single claim. Applicant should note that the Examiner could not locate *In re Weber*, 198 U.S.P.Q. ***332***, but did locate *In re Weber*, 198 U.S.P.Q. 328, which was also cited in *In re Haas*. If the wrong case is being addressed, Applicant is invited to provide a copy of the case such that a proper evaluation of it's holding can be made. First, the holdings in *Weber* and *Haas* were that 35 U.S.C. § 121 does not provide a basis for rejection of claims, and did not address restriction practice. The holdings in *Weber* and *Haas* fail to support Applicant's assertion that section 121 only applies to plural claimed inventions in different claims. For example, if Applicant were to claim "An invention selected from the group consisting of a car, a dog, and a DNA", does this mean that each of these inventions must be examined together because they are in a single claim despite the fact they are clearly directed to distinct inventions?

Claim 42 is drafted as a method of treating one of 6 unrelated diseases or disorders by administration of one or more FGF muteins. Therefore, the claim is drafted as a Markush-type claim. Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, **unless the subject**

matter in a claim lacks unity of invention (emphasis added). *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. In the instant claim, the Markush is not one of compounds, but of diseases/disorders. However, these recited diseases/disorders do not appear to have unity of invention because there is no common feature associated with each or no common utility. Therefore, claim 42 is an improper Markush claim and restriction is proper. Burden is again established on the basis that each disease/disorder requires a separate search in that art revealed for one condition, such as neural injury, would not be art for any of the other conditions, such as heart disease.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 41-42, 48-83, in so far as they encompass methods other than a method of stimulating cell division, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

Claims 39, 54-81 are under consideration in the instant application, in so far as they read on the elected invention.

Priority

4. This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application because the current status of all nonprovisional parent applications referenced should be included. Correction is required.

Specification

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed (i.e. methods ....).

Claim Objections

6. Claims 54-61, 70-74 are objected to because of the following informalities: they are directed to non-elected subject matter and depend from non-elected claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 39, 54-81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of stimulating cell division by administering a

mutein of bFGF comprising the substitution of position 89 with either alanine or tyrosine and the substitution of either of positions 101 or 137 with alanine, does not reasonably provide enablement for a method utilizing a mutein with a substitution of those positions with any neutral amino acid or hydrophobic amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification is directed to mutants of human basic fibroblast growth factor wherein the amino acids at positions 89, 101, and/or 137 are substituted with either a neutral or hydrophobic amino acid and methods of using the disclosed mutants. The specification defines a neutral amino acid as including serine, threonine, alanine, asparagine, glutamine, cysteine, glycine, and non-naturally occurring analogues thereof. The specification defines a hydrophobic amino acid as tyrosine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, methionine, and non-naturally occurring analogues thereof. The instant specification is broader than the enabling disclosure because alanine is the only amino acid which has been substituted as all three positions and tyrosine has only been substituted at position 89 and one of ordinary skill in the art would not find these substitutions predictive of all the amino acids which are encompassed by the claim limitations of neutral or hydrophobic amino acids. The specification exemplifies the substitution of amino acid positions 89, 101 and 137 with alanine, however, one of ordinary skill in the art would not reasonably conclude that this substitution is predictive and exemplary of the other amino acids which are encompassed by the claims. For example, alanine is a small, neutral amino

acid and one would not reasonably conclude that the result obtained with this substitution would be the same as with an amino acid with an acidic side chain, such as aspartate or glutamate, because these are charged amino acids. The substitution of alanine is not predictive of a substitution with cysteine because cysteine is available for disulfide bond formation, and one would expect some odd structural effects from this substitution. Serine and threonine have much larger side chains than alanine, and the substitution with alanine could not be predictive of these amino acids, which may have steric hindrance issues in the structure of bFGF, and therefore, it is not clear what the biological effect of such a mutation would be. Additionally, tyrosine, phenylalanine, and tryptophan, have large aromatic side chains, so structurally, alanine is not predictive of these amino acids. Methionine is a larger amino acid which has a sulfur-containing side chain, and one of ordinary skill in the art would not find alanine predictive of this amino acid. The claims further encompass leucine, isoleucine, valine, proline, which are either structurally larger (leu, ile, val) or structurally dissimilar (pro) than alanine, therefore, one would not find alanine to be predictive of these amino acid substitution. A proteins function is dependent on its structure, and the size and/or charge and/or chemical nature of the amino acids in that protein can dramatically effect the biological functions of protein. The substitution of alanine at the recited positions in the claims resulted in a bFGF protein that acts as a superagonist, however, one cannot predict from the substitution of alanine at these positions what biological property will be possessed by the other substitutions. This is because alanine is not representative of the other amino acids encompassed by the claims.

The issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990), and *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988). A review of *In re Wands* clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the enablement of an invention.

Further, *In re Wands* determined that the repetition of work which was disclosed in the patent application as producing a composition containing an antibody, which is a naturally occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. The instant claims are not limited to naturally occurring compounds and the instant specification does not provide a description of a repeatable process of producing a protein which has the same biological activity as the alanine substitutions. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work described in the instant

application, but a substantial inventive contribution on the part of a practitioner which would involve the determination of which substitutions and combinations of substitutions would result in the biological activity of a superagonist. The decisions of *In re Fisher*, Amgen Inc. v. Chugai, and *In re Wands* have been relied upon in the instant rejection and by the court in a recent CAFC decision, Genentech, Inc. V. Novo Nordisk, 42 USPQ2d, 100 (CAFC 1997) because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of the claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims. For this reason, the claims are not commensurate in scope with the enabling disclosure of the instant specification.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 39, 54-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims encompass the substitution of position 137 with a hydrophobic amino acid, which includes the naturally occurring amino acid of leucine at this position. It is not clear how the substitution of leucine at position 137 with leucine would provide for a mutein, wherein the specification describes a mutein as having an altered property, structural or functional. Therefore, the claims are indefinite for the recitation of mutein when naturally occurring amino acids are encompassed by the claims.

Claim 39 recites "comprising the substitution of a neutral and/or hydrophobic amino acid for one or more of the following". This recitation is confusing because it seems to imply that two amino acids could replace one of the recited amino acids. It would appear that the specification only contemplates single amino acid substitution (i.e. a one for one substitution), but the claim encompasses replacement of one amino acid with potentially two amino acids (both neutral and hydrophobic). Clarification appears to be necessary.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud